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WINTER 2019

Featured Study:

Treatment of Disturbed Sleep in PSP

The Treatment of Disturbed Sleep in persons with Progressive Supranuclear Palsy (PSP) is a remote, six-week clinical trial sponsored by the University of California, San Francisco (UCSF). Researchers hope to answer the question: "Can We Improve Sleep in PSP?"

The study will test the effectiveness of two sleep medications. While there is no traveling to the study site, all participants must have a care partner who is willing to assist.

Sleep can be challenging for people who have been diagnosed with PSP with both insomnia and impaired sleep being common. Prior studies have shown that sleep/waking regulation and REM sleep regulation are disrupted in PSP, leading to profound sleep deprivation without any recuperation the following day.

"Our primary hope is to improve sleep, which is significantly impaired in many with PSP. Maybe by improving sleep, we can also improve general well-being and slow the course of the disease," said Christine M. Walsh, Ph.D., assistant professor of neurology at UCSF. "The quality of life, especially between the participant and the caregiver may also be improved."

The study has a crossover design where all participants will receive two FDA-approved hypnotics, a wake-promoting antagonist and a sleep-promoting agonist, as well as a placebo, Dr. Walsh explained. It's a short trial where participants take each drug for seven nights with a week of no sleep medications in between.

CRITERIA

Initially, participants for this study need to reside in California where doctors at UCSF can prescribe the medications. However study investigators are trying to work with doctors involved with the ALLFTD Study (formerly ARTFL & LEFFTDS), 4 Repeat Tauopathy Neuroimaging Initiative (4RTNI) and other neurologists, which would open the trial to other states. The remote study would still be run through the research team at UCSF with the assistance of a collaborator in the state a participant is living in, Dr. Walsh said.

"We are fully enrolling people from within California," she said. "We want to hear from other people, but there may be a delayed entrance into the study. There already are people affected by PSP in Texas and Alaska who are willing to participate, when this becomes possible."

To qualify, participants must have a PSP diagnosis and they cannot be taking other sleep medications while on the study.

"For the most part if you qualified for some of the (PSP) observation studies, you likely will qualify for ours," she said.

The UCSF team is relying on the participant's neurogist that he or she has PSP. Ideally participants would be co-enrolled in 4RTNI or ALLFTD. However, if

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someone is not enrolled in one of those, they are still encouraged to enroll in this sleep study.

"We're open to working with their local neurologist where they would send the medical records over and our medical fellow [Lawren Vandevrede, M.D., Ph.D.] would look through them, and then they would set up a call with the participant and caregiver to check on the history. We can also evaluate observations made by the neurologist who has examined and treated the participant."

Most importantly, a caregiver is required to take part in the study, to help out in general, and to report on how the participant is doing.

Additionally, the participant needs to be able to communicate on the phone or on a video screen. "We are open to both. We don't need someone to be able to fluently talk; 'yes' and 'no' is sufficient," she explained. "But they need to be willing to stay on a phone or a screen for at least half an hour. We can separate our testing periods into subparts, but they still need to be on with us for approximately two 30-minutes sessions."

All of the standard study assessments will be handled over the phone, with at least one phone call every week.

Some of the questions will be about the participant's mood, cognition, and quality of life, such as: Based on the past week, how are you feeling? Would you choose to continue taking this medication? What side effects have you experienced? Did the medication have any affect on you?

Some people are more sensitive to medications and may experience side effects. However, both drugs are FDA-approved medications that have been used for several years so the investigators are very aware of the possible side effects.

"Having the design that we do, we will be able to track and account for those side effects easier," Dr. Walsh noted.

PSP Sleep Study

Treatment of Disturbed Sleep in Progressive Supranuclear Palsy (PSP)

Previous studies have shown a marked loss of sleep in persons with PSP. In one published paper, on average people with PSP are sleeping approximately four hours a day. And despite sleeping little at night, they have very limited ability to sleep the next day when given opportunities to nap.

"Our study showed that individuals with PSP can't sleep on demand during the day after not sleeping great the night before. They're not having slight nod offs." she said. "Two of our PSP participants slept less than two hours. They remained awake as long as individuals who had a full night's sleep. We found that very concerning and remarkable," she explained.

"You have both a wake-on system and a sleep-on system. The nuclei that are promoting wake-on are not fully spared, but relatively spared in PSP, especially compared to Alzheimer's disease. What we think is happening, is that we have this imbalance where the wake-on system is basically allowed to run free and so it's preventing individuals with PSP from having stable sleep," Dr. Walsh explained. "So it's either preventing them from sleeping initially, like falling asleep, it keeps waking them up during the night, or it has them waking up really early, or a combination of all three."

ALL PEOPLE WITH PSP INVITED

Dr. Walsh said that they are interested in working with people regardless of whether they think they have

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good or bad sleep.

"A lot of times people think that their sleep is too bad or too good and that we're just not interested," she said. "We are interested in everybody."

This study began in June 2019, and is scheduled to end in October 2021.

There is no cost for participating in the study, and people who complete it will receive a $125 prepaid debit card.

Principal investigator is Dr. Thomas Neylan, Professor, In Residence in the Department of Psychiatry at UCSF. Co-investigators, in addition to Dr. Walsh, are Adam L. Boxer, M.D., Ph.D., Endowed Professor in Memory and Aging in the UCSF's Department of Neurology; and Lea T. Grinberg, M.D., Ph.D. Associate Professor in the Memory and Aging Center, Department of Neurology, Weill Institute for Neurosciences at UCSF. Dr. Vandevrede is assisting as neurology fellow. Dr. Neylan and Dr. Walsh co-wrote the study's proposal with several other people.

"This is a very short trial where they're only taking each of these medications for one week so it's just seven nights of treatment. That's where we may not see a full movement on global scale of symptoms because it's a short time," she said. "But that could be the next step if we see that the efficacy of these drugs is good and it's an appropriate medication to give these patients so that we don't have any adverse effects and they are tolerating them well."

READ MORE ABOUT DR. CHRISTINE M. WALSH

LEARN MORE ABOUT THE TREATMENT OF DISTURBED SLEEP IN PSP ON CLINICALTRIALS.GOV

DISTURBED SLEEP IN PSP STUDY

Title: Treatment of Disturbed Sleep in Progressive Supranuclear Palsy (PSP)
ClinicalTrials.gov identifier (NCT number): NCT04014387
Sponsor: University of California, San Francisco
Collaborator: US Department of Veterans Affairs
Funding: Rainwater Charitable Foundation, Tau Consortium

Brief Summary:

Prior research has identified profound sleep disruption in individuals with PSP. Not only were these individuals sleeping relatively short periods at night, they were also not recuperating lost sleep during the day. Research also showed the relative preservation of a series of nuclei key in regulating wake and arousal.

Investigators believe that therapeutically targeting wake promoting centers with a specific medication will improve sleep quality and overall well-being in PSP. To study this, investigators will be doing a double blind, within subject, remote clinical trial with two FDA-approved hypnotics - a wake-promoting antagonist and a sleep-promoting agonist - and a placebo.

Each condition will last 1 week and will be separated by a 1-week washout period on no sleep medications. Investigators will measure sleep patterns and daytime symptoms to determine if either or both medications are safe and effective for treating sleep disturbances and improving overall well-being in PSP.

Study is a U.S. FDA-regulated Drug Product: Yes

STUDY DESIGN

Study Type: Interventional (Clinical Trial)
Estimated Enrollment: 60 participants
Allocation: Randomized

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Intervention Model: Crossover Assignment
Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor
Primary Purpose: Treatment

Official Title: Treatment of Disturbed Sleep in Progressive Supranuclear Palsy (PSP)
Actual Study Start Date: June 2, 2019
Estimated Primary Completion Date: February 15, 2021
Estimated Study Completion Date: October 15, 2021

OUTCOME MEASURES

Primary Outcome Measures:

1. Sleep Efficiency [Time Frame: average each of the 7 nights of treatment for each of the two hypnotic drugs and placebo (weeks 2, 4 and 6) compared to baseline (week 1).]

   Change in sleep efficiency (as measured by actigraphy), this is a percentage of the time spent asleep compared to the total time in bed. The range of scores is 0-100, with higher scores associated with better sleep efficiency.

2. Clinical Global Impression [Time Frame: 7th day of treatment for each of the two hypnotic drugs and placebo (weeks 2, 4 and 6) compared to baseline (week 1).]

   Change in Clinical Global Impression (CGI-C), this is a series of questions for the participant and caregiver which the neurologist utilizes to give a score of disease affects across a series of domains, which produces a single change score referenced to the baseline Clinical Global Impression of Disease Severity (CGI-ds). The range of scores is 1-7, with lower scores associated with better health.

Secondary Outcome Measures:

1. Medication Satisfaction [Time Frame: 7th day of treatment for each of the two hypnotic drugs and placebo (weeks 2, 4 and 6)]

   Differences in satisfaction with the medication being taken. The Medication Satisfaction Scale is a study-specific customized satisfaction questionnaire of 3 questions each with a 5-point likert scale. The total range of scores is 3-15, with higher scores associated with greater medication satisfaction.

   Adverse Events [Time Frame: total of events across the 7 days/nights of treatment for each of the two hypnotic drugs and placebo (weeks 2, 4 and 6) compared to baseline (week 1).]

   The difference in the number of adverse events across each assessment week. The range of scores is 0 - undetermined, with greater scores associated with greater adverse events.

2. Alertness [Time Frame: 7th day of treatment for each of the two hypnotic drugs and placebo (weeks 2, 4 and 6) compared to baseline (week 1)]

   Change in alertness, which is assessed using question 8 of the Mayo Sleep Questionnaire - Informant. The range of scores is 0-10 with higher scores associated with greater alertness.

3. Sleepiness [Time Frame: 7th day of treatment for each of the two hypnotic drugs and placebo (weeks 2, 4 and 6) compared to baseline (week 1).]

   Change in sleepiness, which is assessed using the Epworth Sleepiness Scale. The range of scores is 0-24 with higher scores associated with increased sleepiness.

4. Insomnia [Time Frame: 7th day of treatment for each of the two hypnotic drugs and placebo (weeks

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2, 4 and 6) compared to baseline (week 1).]

Change in subjectively reported insomnia assessed using the Insomnia Severity Index. The range of scores is 0-28 with higher scores associated with increased levels of insomnia.

5. Anxiety [Time Frame: 7th day of treatment for each of the two hypnotic drugs and placebo (weeks 2, 4 and 6) compared to baseline (week 1).]

   Change in anxiety levels assessed using the Generalized Anxiety Disorder - 7 (GAD-7) scale. The range of scores is 0-21 with higher scores associated with greater anxiety.

6. Depression [Time Frame: 7th day of treatment for each of the two hypnotic drugs and placebo (weeks 2, 4 and 6) compared to baseline (week 1).]

   Change in depression assessed using the PHQ-9 scale. The range of scores is 0-27 with higher scores associated with greater depression.

7. Quality of Life [Time Frame: 7th day of treatment for each of the two hypnotic drugs and placebo (weeks 2, 4 and 6) compared to baseline (week 1).]

   Change in quality of life using the PSP Quality of life survey, which assesses subjective quality of life specifically in individuals with Progressive Supranuclear Palsy. The range of scores is 0-100 with higher scores associated with poorer quality of life.

8. Functionality [Time Frame: 7th day of treatment for each of the two hypnotic drugs and placebo (weeks 2, 4 and 6) compared to baseline (week 1).]

   Change in functionality is assessed using the Tau functional scale. This is a questionnaire, which both the patient and caregiver work together to complete. The total range of scores is 0-124 with subscores for "motor experiences of daily living" (0-48 points), "Language/cognitive/behavioral" concerns (0-52) and "Other non-motor experiences of daily living" (0-24). In all cases, greater scores are associated with decreased independent functionality in those domains.

9. Cognition [Time Frame: 7th day of treatment for each of the two hypnotic drugs and placebo (weeks 2, 4 and 6) compared to baseline (week 1)]

   Change in cognition will be assessed using working memory measures of digits forward and digits backward, and executive function measures of categorical fluency and verbal fluency. The range of scores for digits forward and digits backward is 0-16 each, with higher scores indicating better cognition. The likely range of scores for the fluency measures are 0-60 with higher scores associated with better executive function. Rule violations and repetitions are also counted and scored with greater scores in these domains associated with poorer cognition.

10. Slow wave sleep [Time Frame: average of 5th-7th night of treatment for each of the two hypnotic drugs and placebo (weeks 2, 4 and 6) compared to baseline (week 1).]

    Change in slow wave sleep will be assessed using a mobile EEG monitor called the Sleep Profiler (Advanced Brain Monitoring, Inc.). The amount of slow wave sleep will be measured as a percent of total sleep time, so the range of scores will be 0-100, with higher scores associated with greater amounts of slow wave sleep.

Ages Eligible for Study: 18 Year and older (Adult, Older Adult)
Sexes Eligible for Study: All
Accepts Healthy Volunteers: No

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CRITERIA

Inclusion Criteria:

- Male or female ≥18 years of age at baseline.
- Documentation of a Progressive Supranuclear Palsy diagnosis as evidenced by one or more clinical features consistent with the Progressive Supranuclear Palsy phenotype as described in the Movement Disorder Society criteria (Höglinger et al., in press) or the NINDS-SPSP criteria (Litvan et al., 1996).
- Written informed consent (and assent when applicable) obtained from subject or subject's legal representative and ability for subject to comply with the requirements of the study.
- Have a diagnosis of PSP verified through co-enrollment in ARTFL, LEFFTDS or 4RTNI, or can show evidence of an accurate diagnosis of PSP to the satisfaction of the study team doctor (e.g. through review of medical records, and/or specific communication with a known medical doctor).
- Have an active caregiver who is willing and able to participate in this study
- Have a mailing address
- Have access to a phone
- Have stable medications (aside from sleep-modifying medications) for 4 weeks prior to actively starting the study
- Be free of sleep modifying medications for 1 week prior to actively starting the study
- Be willing to maintain a stable sleeping environment and their typical daily schedule for the duration of the 6-week study
- Resides in a U.S. territory or state covered by our research study team.

Exclusion Criteria:

- Are pregnant, breastfeeding, or unwilling to practice birth control if appropriate during participation in the study.
- Presence of a condition or abnormality that in the opinion of the Investigator would compromise the safety of the patient or the quality of the data.
- Presence of a major psychiatric disorder aside from anxiety or depression.
- Presence of a medical condition other than PSP that could account for cognitive deficits (e.g. active seizure disorder, stroke, vascular dementia).
- Presence of current substance abuse or substance dependence.
- Presence of a significant systemic medical illness (e.g. significant cardiovascular, hematologic, renal, or hepatic disease).
- Presence of current medication likely to affect sleep outcomes: benzodiazepine receptor agonists (e.g. Zolpidem), Suvorexant, sedating antipsychotics (e.g. Quetiapine), sedating antihistamines (e.g. Benadryl), low dose sedating antidepressants (e.g. Trazodone, Doxepin), over the counter sleep-inducing medications (e.g. Tylenol-PM), neuroleptics in the phenothiazine and haloperidol families) which 1) the potential participant is not able/willing to stop taking for 1 week prior and for the 6-week duration of the study and/or 2) if removed could have a persistent effect beyond the 1-week wash-out period.
- Presence of insulin-dependent diabetes.
- History of mental retardation.
- Unable to communicate with the research team.

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